☒ Any additional filing fees required, including fees for the presentation of extra claims under 37 CFR § 1.16.

☒ Any additional patent application processing fees under 37 CFR § 1.17 or 1.20(d).

SHOULD ANY DEFICIENCIES APPEAR with respect to this application, including deficiencies in payment of fees, missing parts of the application or otherwise, the U.S. Patent and Trademark Office is respectfully requested to promptly notify the undersigned.

Date: January 22, 2003

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Applicant has discovered stable pharmaceutical formulations containing cyclic amino acids susceptible to degradation and methods for making the same. Stabilizing the cyclic amino acid compounds reduces the rate of degradation and thereby limits the formation of undesirable lactam impurities by re-cyclization reaction. Cyclic amino acid pharmaceutical formulations must limit the quantity of impurities contained therein in order to maintain potency and efficacy.

Claims 1-4, 6-24, 26-44, 53-58, and 60-64 recite pharmaceutical formulations that include one or more stabilizers and one or more amino acids susceptible to formation of a lactam which are sufficiently stable upon storage, even, in the presence of *at least 20 ppm of an anion.* Amino acids that are susceptible to formation of a lactam include, for example, 1-aminomethyl-1-cyclohexaneacetic acid (gabapentin), ethyl 1-aminomethyl-1-cyclohexane acetate, 1-aminomethyl-1-cycloheptaneacetic acid, and n-butyl 1-aminomethyl-1-cycloheptane acetate. See App. para. 23. Stabilizers that inhibit the formation of the lactam include, for example, alcohols, non-volatile liquids such as polyethylene glycol, water miscible liquids or solids, water immiscible liquids or solids, liquid surface active agents, solid surface active agents, antioxidants, ketones, or aldehydes. See App. para. 27.

Applicant's pharmaceutical formulations recited in claims 1-4, 6-24, 26-44, 53-58, and 60-64 overcome the limitation of conventional formulations of not being stable when the formulations contain greater than 20 ppm of an anion. See U.S. Patent No. 6,065,482 to Augart et al. It is thought that formulations having 20 ppm or more of a mineral acid anion do not provide acceptably stable solid dosage forms of cyclic amino acids because the mineral acid anions induce the degradation of the cyclic amino acid to form its corresponding lactam. Traditionally, cyclic amino acid formulations having lactam impurities are purified

by treatment with a mineral acid to convert the undesirable lactam impurity to the pure amino acid form. Conventional techniques control the rate of lactam formation by limiting the amount of residual mineral acid anions present in the pharmaceutical formulation, e.g., *to less than 20 ppm of an anion.* Unfortunately, controlling the amount of residual mineral acid anion is both expensive and time consuming. In contrast to conventional formulations, Applicant's pharmaceutical formulations include *stable* formulations of cyclic amino acids having *greater than 20 ppm of an anion.*

Claims 65, 66, 68-73 provide pharmaceutical formulations that include one or more stabilizers and one or more amino acids susceptible to formation of a lactam which are sufficiently stable upon storage in the presence of less than 20 ppm of electronegative ions.

Claims Rejections - 35 U.S.C. §112,2d para.

In the Office Action, claims 1-4, 6-24, 26-44, 53-58, 60-66, and 68-73 have been rejected 35 U.S.C. §112, 2d para. as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. This rejection is respectfully traversed.

Applicant respectfully disagrees that claims 1-4, 6-24, 26-44, 53-58, 60-66, and 68-73 are indefinite because the term "susceptible" is vague because one skilled in the art would have no difficulty identifying the amino acids that degrade in their solid states to form a lactam. For example, amino acids degrade by a dehydration process that leads to cyclization to a lactam, as described in the specification. Therefore, the art skilled would know whether an amino acid was of the type that was at risk, i.e., susceptible, of degrading to a lactam.

Accordingly, Applicant respectfully requests withdrawal of the objection of claims 1-4, 6-24, 26-44, 53-58, 60-66, and 68-73 under 35 U.S.C. §112, second paragraph.

Claims Rejections - 35 U.S.C. §102(e)

In the Office Action, claims 1-4, 6-24, 26-31, 35-44, 53-58, 60-66, and 68-73 have been rejected under 35 U.S.C. §102(e) as allegedly being unpatentable over U.S. Patent No. 6,294,198 to Vilkov. This rejection is respectfully traversed as the Vilkov patent does not teach every element of the claimed invention.

As will be shown, the Vilkov patent does not teach stable pharmaceutical formulations having at least 20 ppm (greater than or equal to 20 ppm) of an anion as recited in claims 1-4, 6-24, 26-31, 35-44, 53-58, and 60-64. Moreover, the Vilkov patent does not teach a stabilizer that reduces the rate of degradation and thereby limits the formation of undesirable lactams.

The Vilkov patent teaches a pharmaceutical tablet composed of, *inter alia*, gabapentin particles that have been spray coated with a binder solution. The binder solution is used to add cohesion to the particles. The binder solution is prepared by dissolving a binder in a solvent. Binders include water soluble derivatives of cellulose, gelatins, sugars, natural and synthetic gums, polyethylene glycol, pregelatinized starch, povidone, copolyvidone, and waxes. See col. 5, lines 29-33. Solvents include ethanol, isopropyl alcohol, methanol, methylene chloride, and acetone. See col. 5, lines 33-35.

The Vilkov patent does not teach *stable* pharmaceutical formulations having *at least 20 ppm of an anion* because the Vilkov reference does not teach a source of anions. The compositions of gabapentin tablets described in the examples and shown in tables 1, 2, and 3

do not include anions at any concentration. Indeed, the Vilkov patent includes no teaching of anion concentration, or the effect of anion concentration on the stability of the pharmaceutical formulations. Thus, with regard to the anion content and stability, the teaching of the Vilkov patent is limited to formulations stabilized using conventional techniques, such as formulations having less than 20 ppm of an anion, e.g., formulations taught by the Augart patent.

The Vilkov patent does not teach pharmaceutical formulations that include a stabilizer that reduces the degradation of amino acids and thereby limits the formation of undesirable lactams as recited in claims 1-4, 6-24, 26-31, 35-44, 53-58, 60-66, and 68-73. Stabilizers include, for example, a volatile alcohol that is expected to remain in the final dosage form. In contrast to the claimed invention, the Vilkov patent teaches a tablet formed by a spray coating method that actually removes solvents, such as, for example, alcohols, from particles of gabapentin. The spray coating technique includes spraying gabapentin particles with a binder solution and evaporating the solvent in a heated air flow of a fluidized bed. See Col. 9, lines 6-30. The fluidized bed removes the solvent from the gabapentin particles to coat the particles with the binder before preparation of a final dosage form. Thus, because the Vilkov patent teaches formulations wherein the solvent of the binding solution is removed from the formulations, the Vilkov patent does not teach stable pharmaceutical formulations having a stabilizer as recited claims 1-4, 6-24, 26-31, 35-44, 53-58, 60-66, and 68-73.

Accordingly, since the Vilkov patent does not teach all of the elements of Applicant's claims 1-4, 6-24, 26-31, 35-44, 53-58, 60-66, and 68-73, withdrawal of the rejection under 35 U.S.C. §102(e) is requested.

Claims Rejections - 35 U.S.C. §103(a)

In the Office Action, claims 1-4, 6-24, 26-44, 53-58, 60-66, and 68-73 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Vilkov patent. This rejection is respectfully traversed because the cited art does not teach or suggest the claimed invention.

As described above, the Vilkov patent does not teach *stable* pharmaceutical formulations having *at least 20 ppm of an anion* as recited in claims 1-4, 6-24, 26-44, 53-58, 60-64. While the Vilkov specification does not expressly preclude a pharmaceutical formulations having greater than 20 ppm of an anion, there is simply no suggestion for the same. Without such a suggestion, the present claims cannot be found obvious over the Vilkov patent.

As described above, the Vilkov patent does not recognize that anion concentration can affect stability or the benefits of treating cyclic amino acids with a mineral acid, i.e., a source of anions. Conventional techniques, such as those described in the Augart patent, control the rate of lactam formation by limiting the amount of residual mineral acid anions present in the pharmaceutical formulation, e.g., *to less than 20 ppm of an anion*. The Vilkov patent does teach the art skilled any more regarding anion concentration and its effect on stability than the Augart patent.

The Office Action nevertheless asserts that one of ordinary skill in the art would be motivated to modify the teachings of the Vilkov patent to achieve stable pharmaceutical formulations that include one or more amino acids that are susceptible to formation of a lactam, one or more stabilizers that inhibit the formation of the lactam, and *at least 20 ppm of an anion*. However, the Office Action points to no legally sufficient motivation for its proposed modification of the Vilkov patent. Indeed, the prior art suggests that a person of

ordinary skill in the art would *not* assume that using a gabapentin salt in the process taught by the Vilkov patent would yield stable pharmaceutical formulations having greater than 20 ppm of an anion. In fact, the prior art suggests the opposite. See the Augart patent.

Moreover, the Vilkov patent does not provide motivation to modify the Vilkov formulation to include a stabilizer that reduces ionic activity as recited in claims 1-4, 6-24, 26-44, 53-58, 60-66, and 68-73. The stabilizers included in Applicant's pharmaceutical formulations reduce electronegative ionic activity, i.e., electrochemical activity of *anions*, and thereby limit the degradation amino acids. As described above, the Vilkov patent does not teach an anion source, or the effect anions have on the stability of gabapentin formulations. Thus, the Vilkov patent provide motivation to prepare formulations having a stabilizer because the Vilkov patent does not recognize the need for reducing the electrochemical activity of anions.

The burden is on the Examiner to show that the Vilkov process will yield formulations as described in the pending claims. Since there is no suggestion in the prior art of record of pharmaceutical formulations having greater than 20 ppm of an anion there cannot be motivation to modify the cited art to achieve the compositions recited in claims 1-4, 6-24, 26-44, 53-58, and 60-64. Because there is no suggestion in the prior art of pharmaceutical formulations that include a stabilizer there cannot be motivation to modify the cited art to achieve the compositions recited in claims 1-4, 6-24, 26-44, 53-58, 60-66, and 68-73.

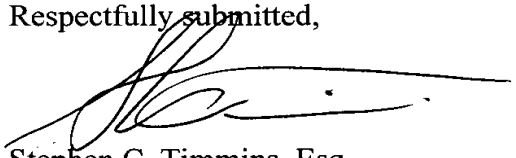
Therefore, the cited references do not teach or suggest all the limitations of the claimed invention. Accordingly, withdrawal of the rejection of claims 1-4, 6-24, 26-44, 53-58, 60-66, and 68-73 under 35 U.S.C. §103(a) is requested.

CONCLUSION

Applicant believes that the foregoing is a full and complete response to the Office Action of record. Accordingly, an early and favorable reconsideration of the rejections and allowance of all of pending claims 1-4, 6-24, 26-44, 53-58, 60-66, and 68-81 are respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE"**.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES

IN THE CLAIMS

Please add new claims 74 - 81.